

Rhizomelic chondrodysplasia punctata: Role of EEG as a biomarker of impending epilepsy

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ABSTRACT

Progressive deterioration of neuroimaging and electroencephalography (EEG) had been described in rhizomelic chondrodysplasia punctata (RCDP); however, serial EEG data showing sequential EEG changes (before and after seizure onset) is lacking. We report a child with a diagnosis of type 1 RCDP, who had a progressive decline in EEG and radiologic findings over a 5 year period. Her first EEG was normal at the age of 8 months. Follow-up EEG at the age of 2 years showed a mild background slowing as well as frequent 1–2 Hz central-parietal spike wave with midline involvement. Just before 3 years of age, she started to seizures, when the EEG showed further worsening with frequent multifocal spikes and bursts of generalized high amplitude spike and spike-wave discharges. The transition of EEG from normal background to the appearance of focal epileptiform abnormality before the seizure onset followed by further deterioration at the seizure onset had not been reported as per our knowledge. This study emphasizes that serial EEGs may provide valuable information about impending seizure activity. Further studies are needed to calculate the lag time between the detection of epileptiform activities and the onset of clinical seizure activities. In addition, research studies are warranted to determine if early (before or at the onset of epileptogenesis rather than after seizure onset) use of replacement therapy or antiepileptic therapy (antiepileptic drugs or diet) can modify epilepsy severity and neurologic prognosis in this devastating disease.

1. Introduction

Rhizomelic chondrodysplasia punctata type 1 (RCDP1) is a peroxisome biogenesis disorder. Majority of the children with severe phenotype develop epilepsy in the first few years of life. Here we reported a child with RCDP1 and described her electroencephalography (EEG) findings since infancy.

2. Case study

A 4-day-old girl with remarkable rhizomelia was referred for further evaluation. She was born at 40 weeks of gestation with a birth weight of 3000 g via spontaneous vaginal delivery after an uncomplicated pregnancy. She was the second child of her nonconsanguineous parents. Her skeletal survey showed shortening of the humeri and stippled epiphyses involving much of the appendicular skeleton with sparing of the axial skeleton (Fig. 1 A). The phytanic acid was elevated and red blood cell plasmalogen was low. Diagnosis of rhizomelic chondrodysplasia punctata (RCDP) type 1 was confirmed with identification of *PEX7* mutations [c.694C > T (p.Arg232X) and c.903 + IG > C (exon 9 splice

donor site)]. A brain magnetic resonance imaging (MRI) was done and was unremarkable (Fig. 1 B).

She was referred to the neurology clinic at the age of 8 months due to high risk of seizures with RCDP1. Her neurological examination showed global severe developmental delays and diffuse weakness and hypotonia. She kept her hands fisted with no attempt to reach or grasp objects and had a paucity of movement with more weakness of bilateral upper extremities. However, she had the ability to visually fix and follow objects and to smile in response to her mother's voice. She also occasionally cooed. Her head circumference was 39.5 cms (–3.2 SD). No seizure-like activity was reported by her mother at that visit. A routine EEG was performed and showed normal background rhythm with no epileptiform activities (Fig. 2 A). She was again seen at the age of 2 years and a repeat EEG was performed to rule out subclinical seizure activity. Her EEG at that time showed a mild slowing of the background as well as frequent 1–2 Hz central-parietal spike wave with midline involvement (Fig. 2 B). Parents denied any seizures at that visit. A prolonged video EEG was performed and showed a similar finding with no subclinical or subtle seizures. Just before 3 years of age, she started to have episodes of tonic stiffening with unresponsiveness.

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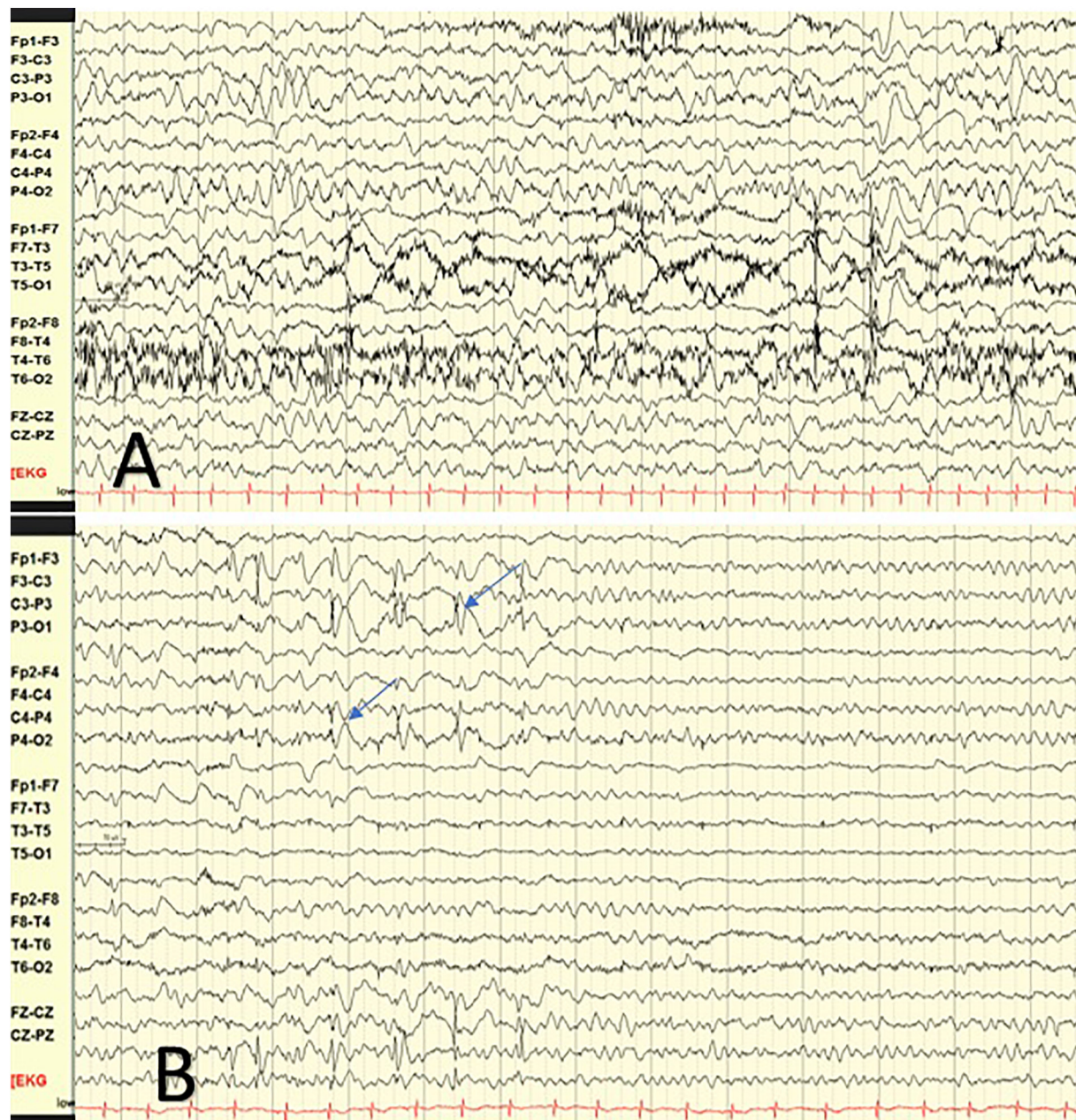


Fig. 1. Changes in the brain MRI in a patient with the severe phenotype of RCDP.

Figure A. Lower limb x-ray image shows punctate epiphyseal calcification, done on day 1 of life B. Coronal T2 MRI shows normal brain MRI with the normal cerebellum at the age of 3 months. C. Coronal T2 MRI shows severe cerebellar atrophy at the age of 3 years 8 months. D. FLAIR T2 axial image shows supratentorial white matter signal abnormalities, most prominent in the bilateral parieto-occipital region.

Initially these episodes were in clusters in every 4–14 days; however, these became more frequent with the occurrence of multiple episodes per day. A repeat EEG showed further worsening of background activity with frequent multifocal spikes and bursts of generalized high amplitude spike and spike-wave discharges. Moreover, several brief tonic seizures were also captured (Fig. 2 C-D). Brain MRI was repeated and showed marked cerebellar volume loss and abnormal supratentorial white matter T2/FLAIR signal hyperintensity (Fig. 1 C-D). Levetiracetam was started with gradual incrementing dose with minimal benefit.

During the last follow-up at the age of 4 years, she continued to have daily multiple brief tonic seizures. The family declined aggressive medication management due to poor neurologic prognosis associated with RCDP. She continued to receive different development therapies.

She had frequent respiratory infections over the prior year and also received a gastrostomy tube for worsening dysphagia.

3. Discussion

RCDP is a disorder of peroxisomal metabolism, with an estimated incidence of 1:100000 [1]. The severe RCDP phenotype is characterized by typical facial appearance, congenital cataracts, rhizomelia, transient periarticular calcification, arthrogenic contractures, and severe developmental impairment [2]. The most common type, type 1, is caused by mutations in the *PEX7* gene. In this type, enzymes are depleted due to a failure to be transported inside the peroxisomes, which leads to stoppage of several metabolic reactions such as the breakdown of fatty acids and synthesis of lipids. An increased phytanic acid level and a

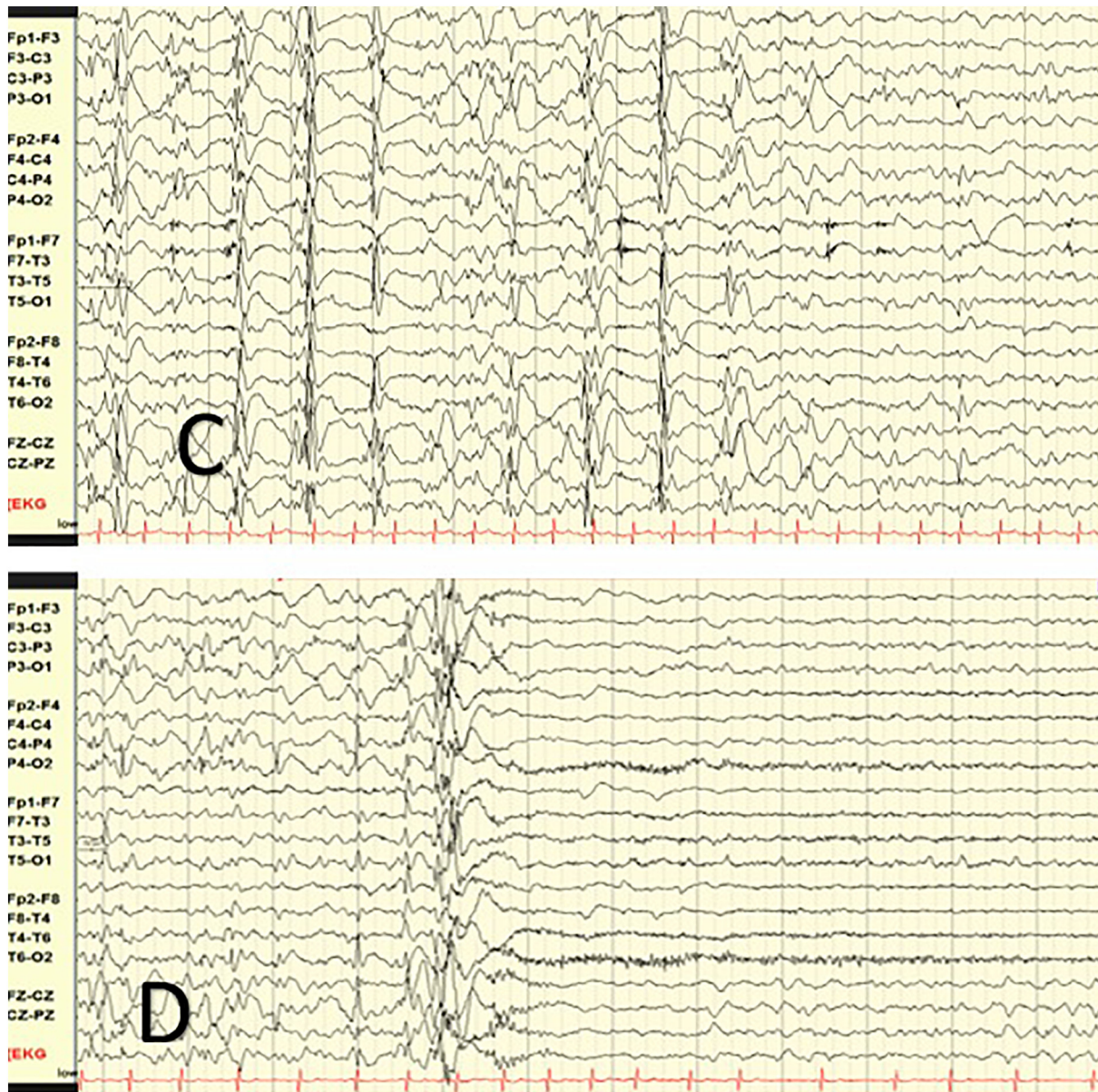


Fig. 2. Changes in the EEG pattern in a patient with the severe phenotype of RCDP.

Fig. A shows EEG at 8 months: Normal background frequency and amplitude (left and right posterior dominant rhythms are shown with arrows; sensitivity 10 uV/mm). Fig. B shows EEG at 3 years: Independent and dependent (arrows) central-parietal epileptiform discharges, but the persistence of normal EEG background. Fig. C. EEG at 4 years: Very high amplitude, disorganized high amplitude background, loss of posterior dominant rhythm, generalized high amplitude slow spike and polyspike wave discharges (Sensitivity of 30 uV/mm). Fig. D shows EEG changes during a tonic seizure with burst of polyspike wave discharge followed by electrodecrement.

Bipolar, anterior-posterior montages (left central, right central, left temporal, right temporal, and then midline chains, 4 channels each).

decreased concentration of plasmalogen (key constituents of neuronal membranes) are seen due to deficient breakdown and synthesis process, respectively.

Progressive deterioration of EEG occurs in RCDP, but serial EEG studies during seizure-free states have not been performed in this population. Previous reports of EEG findings showed a normal/mildly abnormal background evolved to a moderate/severe abnormality. However, the transition of normal EEG to focal epileptiform abnormality before the seizure onset followed by further deterioration at the seizure onset had not been reported as per our knowledge. Bams-Mengerink et al. reported neurologic manifestations of the largest cohort of RCDP patients [1]. In that cohort, 11 out of 12 patients with severe phenotype had epilepsy. The median age of seizure onset was at around 2.5 years. Myoclonic seizures were the most common type.

Generalized tonic-clonic, myoclonic-tonic, atypical absence were the other reported types. Seizures were intractable and valproate was the most commonly used antiepileptic medication in that cohort. Out of these 12 patients, a deterioration of EEG pattern was seen in 7 patients. In this cohort, patients with the severe phenotype that did not show epileptiform discharges on EEG were all less than one year old. However, epileptogenic changes several months prior to the seizure onset were not described. Natural history studies were not also particularly helpful regarding the description of EEG. Most often nonspecific generalized changes were described. [3] Takahashi et al. reported a sequential change in EEGs from bilateral diffuse 75-uV, 4-Hz activity at the age of 7 months that evolved to bilateral diffuse synchronous spike with slow waves and bilateral independent multifocal spikes at the age of 2 years 4 months [4]. However, again this EEG evolution in respect

to clinical seizure activity was undefined.

Currently, there is not a specific guideline regarding obtaining EEG in RCDP patients prior to seizure onset. In most situations, EEG is obtained at the time of seizure onset or in the presence of a spell suspicious for seizures. However, serial EEGs may provide valuable information about impending seizure activity. For example, infants with tuberous sclerosis complex showed an average interval between two to three months from the time that EEG demonstrated epileptiform activity and the onset of seizures. Wu et al. reported 100% positive predictive value of the epileptiform discharges for subsequent epilepsy in this particular cohort [5]. Moreover, Jozwiak et al. reported that preventive vigabatrin treatment of infants with tuberous sclerosis and multifocal activity on EEG lowered the incidence of drug-resistant epilepsy and mental retardation [6]. Presymptomatic treatment of seizure has not been explored in RCDP patients. White et al. reported 2 patients in their cohort who had a remarkable response to the ketogenic diet; however, information regarding EEG changes from the ketogenic diet is lacking [3].

Regarding RCDP, homozygous mutation of L292X in PEX7 is most commonly associated with a severe phenotype, while the missense mutation H285R can be detected in the patients with the milder phenotype. Besides RCDP, other disorders of peroxisome biogenesis, such as Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), acyl-CoA oxidase deficiency (AOXD), bifunctional enzyme deficiency (BFED) can present with early-onset seizures [9]. Patients with ZS or AOXD may have focal motor seizures. Interictal EEGs of the patients with ZS show infrequent bilateral independent multifocal spikes, predominantly in the frontal motor cortex and its surrounding regions. However, the EEGs of patients with AOXD may have interictal fast theta activity, predominantly in the frontocentral regions. Patients with BFED also develop intractable focal motor and myoclonic seizures in early infancy. Interictal EEGs of patients with BFED have bilateral independent multifocal spikes with evolution to bilateral diffuse high-voltage slow waves or hysarrhythmia pattern. Patients with NALD develop intractable tonic seizures or epileptic spasms. Interictal EEGs show high-voltage slow waves and bilateral independent multifocal spikes, evolving to diffuse electrovoltage suppression.

4. Conclusion

Management of RCDP is primarily supportive and most affected infants die within the first decade of life because of respiratory complications [7]. However, plasmalogen replacement therapy may be available in the recent future to modify the disease course [8]. EEG as a biomarker specifically related to neurologic outcome may be particularly helpful in that situation. Further prospective studies are required to evaluate serial EEGs as a biomarker for subsequent epilepsy in the RCDP population to demonstrate the feasibility and importance of close EEG surveillance. It is also necessary to know if there is a critical window of time between the emergence of epileptiform discharges and clinical seizure onset which provides a unique opportunity to investigate potentially disease-modifying antiepileptogenic treatment (ketogenic diet, plasmalogen replacement therapy, and antiepileptic medications) strategies in this population.

Supplementary data to this article can be found online at <https://>

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Declaration of Conflicting Interests

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Contribution

Debopam Samanta is responsible for conceptualization, investigation, writing and reviewing the original draft of this paper.

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